DETAILED ACTION

Claims 1, 3-20 are pending .

Receipt and consideration of Applicants' amended claim set and remarks/arguments filed on 05/08/2009 is acknowledged. Claim 2 is cancelled an claims 1, 3, 4 and 6 are amended. Claims 1, 3-18 are under consideration, claims 19-20 are withdrawn from consideration as being drawn to unelected invention.

Applicants' arguments, filed 05/08/2009 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Election/Restrictions

Applicant's agreement with the examiner's decision to examine new Group I (original Group I and II rejoined) in the reply filed on 05/08/2009 is acknowledged.

Restriction for examination purposes as indicated is proper and the restriction requirement is made final.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Rejection of claims 1, 5-14, 17, 18 under 35 U.S.C. 102(b) as being anticipated by Tuite et al (Expert opinion in investigational Drugs, August, 12(8), pages: 1335-1352, 2003. referenced in Instant IDS) is maintained for reasons of record restated below.

Currently amended claim 1 incorporates the limitations of previously submitted now cancelled claim 2 specifically the limitations "(a) identifying a subject (I) without symptoms of Parkinson's disease but with an increased risk of developing Parkinson's disease or (II) with early symptoms of Parkinsons disease……"

Tuite teaches that in Phase III double-blind, randomized placebo controlled parallel group clinical trials was conducted in 316 patients with early stages of Parkinson's disease. Applicant's recite in the instant disclosure [0046], that individuals with early symptoms of Parkinson's disease are to be understood in particular as individuals in whom at least three of the four cardinal symptoms are not yet present or are only rudimentarily or partially present, but who manifest diagnostically usable early clinical, clinical/biochemical and/or clinical/physical symptoms. Accordingly, as defined by the applicant's disclosure, population of subjects in Tuite's study are at early stages of Parkinson's and would therefore fit into the subject population instantly claimed. Additionally, Tuite teaches that rotigotine appears to be efficacious as monotherapy in

de novo patients (early stage Parkinson's). De Novo patients are patients who have not been treated with any other anti PD medications and as such would be patients at very early stage of the disease and as such fall under the subject population instantly claimed.

Original rejection

Tuite reviews recent developments in the pharmacological treatment of Parkinson's disease. Tuite discloses Rotigotine as a selective D2 receptor agonist that is currently in Phase II and III clinical trials (PATCH study). The study was conducted to compare efficacy, safety and tolerability of four doses of rotigotine (4.5 mg, 9 mg, 13.5 mg, 18 mg) and all doses were delivered using up to four patches. Tuite teaches that in Phase III double-blind, randomized placebo controlled parallel group clinical trials was conducted in 316 patients with early stages of Parkinson's disease. The primary end point was a change from baseline in UPDRS part II (ADL) and III (motor) scores at week 11 of treatment and the secondary end points included UPDRS mental, ADL and motor subscale scores and the Hoehn and Yahr stage from baseline to week 11. Rotigotine produced linear and dose related improvement in UPDRS scores relative to baseline up to a dose of 13.5 mg. In summary Tuite teaches that this rotigotine patch study produced a statistically significant reduction of combined ADL and motor scores in Parkinson's disease subjects (page 1342, left col., Last paragraph to right col., 1st paragraph). Tuite additionally discloses that Rotigotine, a dopamine agonist delivered transdermal, delivers steady-state plasma concentrations within 24 hours of patch

application and may be beneficial as adjunctive therapy in patients with motor fluctuations and rotigotine appears to be efficacious as monotherapy in de novo patients (early stage Parkinson's) (page 1354, right col. Last paragraph to page 1343, left col., 1st paragraph).

In individuals with idiopathic PD, approximately 60% of the nigrostriatal neurons of the substantia nigra (SN) are degenerated before neurologists can establish the diagnosis as evidenced by Becker et al (abstract) Accordingly, all the individuals in the study recited by Tuite who had early stages of PD inherently had approximately 60% loss of the substantia nigra. The instant claim 14, recites the limitation less than 60% and absence of the actual range which defines the term "less than" the term approximately anticipates the limitation. In accordance with MPEP §2131.01, it is proper to rely upon a secondary reference for a rejection under 35 U.S.C. 102, provided that the additional reference is relied upon to demonstrate that a characteristic or property not disclosed by the primary reference is, in fact, inherent.

Response to arguments submitted on 05/22/2009:

Applicant traverses the above rejection on the ground that Tuite does not disclose, either expressly or inherently every limitation of the claim specifically, Tuite does not disclose identifying a subject (i) without symptoms of Parkinson's disease (PD) but with an increased risk of developing PD or (ii) with early symptoms of Parkinson's disease but not exhibiting at least three of four cardinal symptoms of PD.

Applicant's traversal arguments for this rejection have been fully considered, but are not found to be persuasive.

As stated above, Tuite teachings that in Phase III double-blind, randomized placebo controlled parallel group clinical trials was conducted in 316 patients with **early stages of Parkinson's disease and that** that rotigotine appears to be efficacious **as monotherapy in de novo patients (early stage Parkinson's) anticipates the new limitations of instant claim 1** as the patient population of Shoulson fits into the definition of the "individuals with early symptoms of Parkinsons disease" defined in the instant disclosre [0046] and the Hahn's score which fits into the definition defined in Table 2 of the instant disclosure

Applicants argue that the alleged findings of inherent anticipation with reference to claim 14 fails, since claim 14 embody all the limitation of claim 1. But as stated above, the new limitations of claim1 are also anticipated by Tuite and as such the subject population in Tuite's study who are in early stages of PD, absence of any evidence to contrary, would also includes those individuals with less than 60% dopaminergic cell loss.

Rejection of claims 1, 5-13, 15-18 under 35 U.S.C. 102(b) as being anticipated by Shoulson (Principal investigator) et. al. (Archives Neurology, Vol. 60, December 2003, 1721-1728, Published 2nd Monday of the month which would be 12/13/2003) is maintained for reasons of record restated below.

Currently amended claim 1 incorporates the limitations of previously submitted now cancelled claim 2 specifically the limitations "(a) identifying a subject (I) without symptoms of Parkinson's disease but with an increased risk of developing Parkinson's disease or (II) with early symptoms of Parkinson's disease……"

Shoulson (principal investigator as recited on page 1726) and his study group disclose a controlled trial of Rotigotine Monotherapy in **Early Parkinson's disease (PD) and the study was conducted in patients with early PD** who were diagnosed as having idiopathic PD and had a **Hoehn and Yahr stage of 3.** Moreover, Shoulson teaches that **rotigotine did not show statistically significant improvement in advanced PD** and will have to be administered with other drugs in advanced PD.

Applicant's recite in the instant disclosure [0046], that individuals with early symptoms of Parkinson's disease are to be understood in particular as individuals in whom at least three of the four cardinal symptoms are not yet present or are only rudimentarily or partially present, but who manifest diagnostically usable early clinical, clinical/biochemical and/or clinical/physical symptoms. Additionally, applicants define in Table 2, that a Hahn's score of less than 3 have very mild bilateral or unilateral disease. As such it is implicit that the subject population in Shoulson's study, fall under the instantly defined parameters as recited above and therefore the instant claims are anticipated by the Shoulson.

Original Rejection:

Shoulson (principal investigator as recited on page 1726) and his study group disclose a controlled trial of Rotigotine Monotherapy in Early Parkinson's Disease (PD). The study was conducted to determine the efficacy, safety, and tolerability of rotigotine in patients with early PD who required but were not yet receiving other dopaminergic therapy (abstract). Eligible subjects for the study included men and women older than 30 years who were diagnosed as having idiopathic PD and had a Hoehn and Yahr stage of 3 or less. The placebo-controlled clinical trial demonstrated that rotigotine administered transdermally at dosages ranging from 4.5 to 18.0 mg/d was safe and generally well tolerated for up to 11 weeks in subjects with early PD. The study also defined the minimum effective dosage of rotigotine in the 9.0- to 13.5-mg range and demonstrated a dose-response relationship among the active treatment groups up to 13.5 mg, with a plateau in the therapeutic effect occurring between 13.5 and 18.0 mg. Transdermal rotigotine treatment produced clinical improvement in parkinsonian symptoms (as measured by the change in motor and ADL UPDRS score between baseline and 11 weeks of treatment) comparable to that reported after administration of the dopamine agonists pramipexole and ropinirole. Table 1 on page 1724 lists the baseline characteristics by treatment groups where patients with UPDRS score for mental and ADL at less than 10. Additionally this study confirms the preliminary data that a dopamine agonist can be effectively and safely delivered via transdermal administration.

In individuals with idiopathic PD, approximately 60% of the nigrostriatal neurons of the substantia nigra (SN) are degenerated before neurologists can establish the

diagnosis as evidenced by Becker et al (abstract) accordingly, all the individuals in Shoulson's study who had idiopathic PD inherently had approximately 60% loss of the substantia nigra. The instant claim 14, recites the limitation less than 60% and absence of the actual range which defines the term "less than" the term approximately anticipates the limitation. In accordance with MPEP §2131.01, it is proper to rely upon a secondary reference for a rejection under 35 U.S.C. 102, provided that the additional reference is relied upon to demonstrate that a characteristic or property not disclosed by the primary reference is, in fact, inherent.

Response to arguments submitted on 05/22/2009:

Applicant traverses the above rejection on the ground that Shoulson study does not include subjects as identified in the method of amended Claim 1, i.e. A subject (i) without symptoms of Parkinson's disease (PD) but with an increased risk of developing PD or (ii) with early symptoms of Parkinson's disease but not exhibiting at least three of four cardinal symptoms of PD.

Applicant's traversal arguments for this rejection have been fully considered, but are not found to be persuasive.

As stated above Shoulson (principal investigator as recited on page 1726) teachings that his study group involves a controlled trial of Rotigotine Monotherapy in **Early Parkinson's Disease (PD) and the patients with early PD** who were diagnosed as having idiopathic PD had a **Hoehn and Yahr stage of 3 anticipates the instant claims** as the patient population of Shoulson fits into the definition of the "individuals

with early symptoms of Parkinson's disease" defined in the instant discloser [0046] and the Hahn's score which fits into the definition defined in Table 2 of the instant disclosure. Applicants argue that the alleged findings of inherent anticipation with reference to claim 14 fails, since claim 14 embody all the limitation of claim 1. But as stated above, the new limitations of claim1 are also anticipated by Tuite and as such the subject population in Tuite's study who are in early stages of PD, absence of any evidence to contrary, would also includes those individuals with less than 60% dopaminergic cell loss.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Rejection of claims 1 and 3-18 under 35 U.S.C. 103(a) as being unpatentable over Tuite et al (Expert opinion in investigational Drugs, 12(8), pages: 1335-1352, 2003) as evidenced by Becker et al.(J. Neuorol., 249(suppl.3) III/40-III/48, 2002, referenced in instant IDS) further in view of Double et al. (WO 02/31499, referenced in instant IDS) and Guttman (Canadian Medical Association Journal, 168 (3), 2003, 293-301, referenced in instant IDS) is maintained for reasons of record restated below.

Currently amended claim 1 incorporates the limitations of previously submitted now cancelled claim 2 specifically the limitations "(a) identifying a subject (I) without symptoms of Parkinson's disease but with an increased risk of developing Parkinson's disease or (II) with early symptoms of Parkinson's disease……"

Tuite teaches that in Phase III double-blind, randomized placebo controlled parallel group clinical trials was conducted in 316 patients with early stages of Parkinson's disease. Applicant's recite in the instant disclosure [0046], that individuals with early symptoms of Parkinson's disease are to be understood in particular as

individuals in whom at least three of the four cardinal symptoms are not yet present or are only rudimentarily or partially present, but who manifest diagnostically usable early clinical, clinical/biochemical and/or clinical/physical symptoms. Accordingly, as defined by the applicant's disclosure, population of subjects in Tuite's study are at early stages of Parkinson's and would therefore fit into the subject population instantly claimed. Additionally, Tuite teaches that rotigotine appears to be efficacious as monotherapy in de novo patients (early stage Parkinson's). De Novo patients are patients who have not been treated with any other anti PD medications and as such would be patients at very early stage of the disease and as such fall under the subject population instantly claimed.

Original Rejection:

Tuite reviews recent developments in the pharmacological treatment of Parkinson's disease (PD). Tuite discloses Rotigotine as a selective D2 receptor agonist that is currently in Phase II and III clinical trials (PATCH study). The study was conducted to compare efficacy, safety and tolerability of four doses of rotigotine (4.5 mg, 9 mg, 13.5 mg, 18 mg) and all doses were delivered using up to four patches. Tuite teaches that in Phase III double-blind, randomized placebo controlled parallel group clinical trials was conducted in 316 patients with early stages of Parkinson's disease. The primary end point was a change from baseline in UPDRS part II (ADL) and III (motor) scores at week 11 of treatment and the secondary end points included UPDRS mental, ADL and motor subscale scores and the Hoehn and Yahr stage from baseline to week 11. Rotigotine produced linear and dose related improvement in

UPDRS scores relative to baseline up to a dose of 13.5 mg. In summary Tuite teaches that this rotigotine patch study produced a statistically significant reduction of combined ADL and motor scores in Parkinson's disease subjects (page 1342, left col., Last paragraph to right col., 1st paragraph). Tuite additionally discloses that Rotigotine, a dopamine agonist delivered transdermal, delivers steady-state plasma concentrations within 24 hours of patch application and may be beneficial as adjunctive therapy in patients with motor fluctuations and rotigotine appears to be efficacious as monotherapy in de novo patients (early stage Parkinson's) (page 1354, right col. Last paragraph to page 1343, left col., 1st paragraph). Tuite additionally teaches in a study in subjects with advanced PD no significant difference between rotigotine and placebo was observed (page 1343, left col. , 3rd paragraph) and that rotigotine use in advanced PD patients also requires additional medications to alleviate symptoms, which may include concurrent orally administered dopamine agonists (page 1343, left col., 1st paragraph).

In individuals with idiopathic PD, approximately 60% of the nigrostriatal neurons of the substantia nigra (SN) are degenerated before neurologists can establish the diagnosis as evidenced by Becker et al (abstract) Accordingly, all the individuals in clinical trail described by Tuite with early PD of inherently had approximately 60% loss of the substantia nigra. The instant claim 14, recites the limitation less than 60% and absence of the actual range which defines the term "less than" the term approximately anticipates the limitation.

Tuite et al do not specifically recite the absence of at least three of the four cardinal symptoms of Parkinson's disease and is silent to the involvement of mutation in the PARK gene and/or modifications to the alpha synuclein or neuromelanine pattern.

Double et al. teaches the method of detecting neurodegenerative diseases such as Parkinson's disease in a subject comprising testing the subject for an indicator of release of neuromelanin from cells in the brain (abstract). Double et al also teaches that in classical or idiopathic Parkinson's disease at least 65% of total substantia nigral dopaminergic neurons are lost prior to onset of the classical clinical symptoms of the disease and the triad of motor symptoms, tremor, rigidity and bradykinesia typify the onset of the clinical phase of the disease during which the rate of loss of the remaining 35% of dopaminergic cells is significantly slower than during the preclinical phase (page 7, lines 13-17) Double et. al. teaches that neuromelanin is a complex polymer pigment believed to be formed from oxidized dopamine products within the dopaminergic neurons of the substantia nigra and neuromelanin usually occurs as granule which can be seen in the cell body, but as a consequence of cell death neuromelanin is released into the extracellular space (oage2, lines 4-9). Double et al provides a method of detecting a neurodegenerative disease in a subject comprising testing the subject for an indicator release of neuromelanin cells in the brain, wherein a positive test is indicative of death of brain cells containing neuromelanin and is characterized by an elevated level of the indicator of release of neuromelanin compared to control values (page 2, lines 10-14). Double et al. additionally teaches that the identification of this specific

marker provides a means for detecting the disorders characterized by the death of these cells, even prior to the onset of clinical symptoms (page 2, lines 15-17).

Guttman et al. teaches that Parkinson's disease is a progressive neurological disorder characterized by rest tremor, bradykinesia, rigidity and postural instability and the cause is unknown but evidence suggests that it may be due to a combination of environmental and genetic factors (abstract). Guttman teaches that eight genetic loci for monogenic forms of Parkinson's disease have been reported (page 295, left col. 2md paragraph and table 2).Guttman further teaches that in autosomal dominant Parkinson's disease 2 missense mutations in the α-synuclein gene (PARL1) were identified and in pedigree's with autosomal recessive early onset parkinsonism, a wide variety of mutations in the parkin gene (PARK2) were found in about 59% of the families, in which at least one of the affected siblings developed symptoms at or before 45 years of age (page 295, left col., 2nd paragraph). Finally, in table 2 Guttman lists the genetically defined forms of Parkinson's disease and parkinsonism which involves gene mutations **PARK genes 1-8** with their specific Gene involved and its clinical characteristics (page 296, table 2).

It would have been obvious to one of ordinary skill in the art to employ rotigotine in prophylactic treatment of Parkinson's disease because rotigotine is effective for the treatment of Parkinson's disease as taught by Tuite et al **early stages of the disease.** Moreover, Tuite teaches that rotigotine did not show statistically significant improvement in advanced PD and will have to be administered with other drugs in advanced PD. Becker, Double et al and Guttman et al teaches the various diagnostic parameters in

determining the onset of Parkinson's disease. With regard to the specified subject population not exhibiting symptoms of Parkinson, but having a high risk set forth in claims 2 not yet having at lest three of four cardinal symptoms including bradykinesia, resting tremors, rigor etc..; a patient having one or more clinical symptoms including movement anomalies set forth in claim 3 a mutation in PARK-gene set forth and/or alternations in the alpha-synuclein or neuromelanin pattern set forth in claim 4; a loss of less than 60% of dopaminergic cells in the substantial nigra set forth in claim 14; a UPDRS score of less than 10 set forth in claim 15; and a Hohn-Yahr score of 0 or 1 set forth in claim 16, they are all obvious because they are all the current evaluation parameters for determining the stages and diagnostic assessment of Parkinson's disease as well known by the above references. One of ordinary skill in the art would promptly evaluate those patients at risk or in at early stages of Parkinson's disease in order to avoid failing of treating Parkinson's disease at their advanced stage. Accordingly, an ordinarily skilled artisan would be motivated to develop a method of treatment of Parkinson's disease at its early stages with rotigotine with a reasonable expectation of success since it has been shown to provide effective decrease in the progression of disease as evidenced by the clinical trials in the prior art.

Response to arguments submitted on 05/22/2009:

Applicant traverses the above rejection on the ground that Tuite study does not include subjects as identified in the method of amended Claim 1, i.e. A subject (i) without symptoms of Parkinson’s disease (PD) but with an increased risk of developing PD or (ii) with early symptoms of Parkinson’s disease but not exhibiting at least three of

four cardinal symptoms of PD which is also not taught by other references used in the rejection i.e. Guttman, Double, or Becker.

Applicant's traversal arguments for this rejection have been fully considered, but are not found to be persuasive.

Tuite teaches the utility of rotigotine in subjects displaying early stages of Parkinson's who as defined by the instant specification are that individuals are to be understood in particular as individuals in whom at least three of the four cardinal symptoms are not yet present or are only rudimentarily or partially present, but who manifest diagnostically usable early clinical, clinical/biochemical and/or clinical/physical symptoms [0046], Tuite with his teachings that Rotigotine is useful as Monotherapy in de-novo PD patients, and with suggestions of modes of therapy and dosage provides an ordinarily skilled artisan ample suggestions and motivation to test the efficacy of rotigotine in patients as prophylactic treatment.. As stated by the applicant, prophylactic treatment methods for Parkinson's disease are still unpredictable and there are no therapies available currently which delay the progression of PD. This fact in itself, supported by the positive results shown by Tuite in early stage PD treatment would motivate an artisan skilled in the pharmacological art to test if the rotigotine would provide any prophylactic benefits. Identification of potential PD markers is well known in the art as taught by Guttman and Double. With that knowledge and knowledge of UPDRS Score and Hoehn Scores, an ordinarily skilled artisan would easily be able to identify a subject at risk of getting PD or in the early stages of PD and with suggestions

provided by Tuite will have a reasonable expectation of success in treating such subjects.

Rejection of claims 1 and 3-18 under 35 U.S.C. 103(a) as being unpatentable over Shoulson et al (Principal investigator) et al (Archives Neurology, Vol. 60, December 2003, 1721-1728) , as evidenced by Becker et al.(J. Neuorol., 249(suppl.3) III/40-III/48, 2002, referenced in instant IDS) further in view of Double et al. (WO 02/31499, referenced in instant IDS) and Guttman (Canadian Medical Association Journal, 168 (3), 2003, 293-301, referenced in instant IDS) is maintained for reasons of record restated below.

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Shoulson (principal investigator as recited on page 1726) and his study group disclose a controlled trial of Rotigotine Monotherapy in **Early Parkinson's disease (PD) and the study was conducted in patients with early PD** who were diagnosed as having idiopathic PD and had a **Hoehn and Yahr stage of 3.** . Moreover, Shoulson

teaches that **rotigotine did not show statistically significant improvement in advanced PD** and will have to be administered with other drugs in advanced PD

Applicant's recite in the instant disclosure [0046], that individuals with early symptoms of Parkinson's disease are to be understood in particular as individuals in whom at least three of the four cardinal symptoms are not yet present or are only rudimentarily or partially present, but who manifest diagnostically usable early clinical, clinical/biochemical and/or clinical/physical symptoms. Additionally, applicants define in Table 2, that a Hahn's score of less than 3 have very mild bilateral or unilateral disease. As such it is implicit that the subject population in Shoulson's study falls under the instantly defined parameters.

Original Rejection:

Shoulson (principal investigator as recited on page 1726) and his study group teach a controlled trial of Rotigotine Monotherapy in Early Parkinson's Disease (PD). The study was conducted to determine the efficacy, safety, and tolerability of rotigotine in patients with early PD who required but were not yet receiving other dopaminergic therapy (abstract). Eligible subjects for the study included men and women older than 30 years who were diagnosed as having idiopathic PD and had a Hoehn and Yahr stage of 3 or less. The placebo-controlled clinical trial demonstrated that rotigotine administered transdermally at dosages ranging from 4.5 to 18.0 mg/d was safe and generally well tolerated for up to 11 weeks in subjects with early PD. The study also defined the minimum effective dosage of rotigotine in the 9.0- to 13.5-mg range and demonstrated a dose-response relationship among the active treatment groups up to

13.5 mg, with a plateau in the therapeutic effect occurring between 13.5 and 18.0 mg. Transdermal rotigotine treatment produced clinical improvement in parkinsonian symptoms (as measured by the change in motor and ADL UPDRS score between baseline and 11 weeks of treatment) comparable to that reported after administration of the dopamine agonists pramipexole and ropinirole. Table 1 on page 1724 lists the baseline characteristics by treatment groups where patients with UPDRS score for mental and ADL at less than 10 were treated. Additionally this study confirms the preliminary data that a dopamine agonist can be effectively and safely delivered via transdermal administration. Shoulson additionally teaches that an initial trial of rotigotine in patients with advanced PD with motor fluctuations showed a reduction in off time in treated subjects, but the magnitude of change failed to reach statistical significance when compared with placebo.

In individuals with idiopathic PD, approximately 60% of the nigrostriatal neurons of the substantia nigra (SN) are degenerated before neurologists can establish the diagnosis as evidenced by Becker et al (abstract) Accordingly, all the individuals in Shoulson's study with idiopathic PD of inherently had approximately 60% loss of the substantia nigra. The instant claim 14, recites the limitation less than 60% and absence of the actual range which defines the term "less than" the term approximately anticipates the limitation.

Shoulson et al do not specifically recite the presence/absence of at least three of the four cardinal symptoms of Parkinson's disease and is silent to the involvement of

mutation in the PARK gene and/or modifications to the alpha synuclein or neuromelanine pattern.

Double et al. teaches the method of detecting neurodegenerative diseases such as Parkinson's disease in a subject comprising testing the subject for an indicator of release of neuromelanin from cells in the brain (abstract). Double et al also teaches that in classical or idiopathic Parkinson's disease at least 65% of total substantia nigral dopaminergic neurons are lost prior to onset of the classical clinical symptoms of the disease and the triad of motor symptoms, tremor, rigidity and bradykinesia typify the onset of the clinical phase of the disease during which the rate of loss of the remaining 35% of dopaminergic cells is significantly slower than during the preclinical phase (page 7, lines 13-17) Double et. al. teaches that neuromelanin is a complex polymer pigment believed to be formed from oxidized dopamine products within the dopaminergic neurons of the substantia nigra and neuromelanin usually occurs as granule which can be seen in the cell body, but as a consequence of cell death neuromelanin is released into the extracellular space (oage2, lines 4-9). Double et al provides a method of detecting a neurodegenerative disease in a subject comprising testing the subject for an indicator release of neuromelanin cells in the brain, wherein a positive test is indicative of death of brain cells containing neuromelanin and is characterized by an elevated level of the indicator of release of neuromelanin compared to control values (page 2, lines 10-14). Double et al. additionally teaches that the identification of this specific marker provides a means for detecting the disorders characterized by the death of these cells, even prior to the onset of clinical symptoms (page 2, lines 15-17).

Guttman et al. teaches that Parkinson's disease is a progressive neurological disorder characterized by rest tremor, bradykinesia, rigidity and postural instability and the cause is unknown but evidence suggests that it may be due to a combination of environmental and genetic factors (abstract). Guttman teaches that eight genetic loci for monogenic forms of Parkinson's disease have been reported (page 295, left col. 2md paragraph and table 2).Guttman further teaches that in autosomal dominant Parkinson's disease 2 missense mutations in the α-synuclein gene (PARK1) were identified and in pedigree's with autosomal recessive early onset parkinsonism, a wide variety of mutations in the parkin gene (PARK2) were found in about 59% of the families, in which at least one of the affected siblings developed symptoms at or before 45 years of age (page 295, left col., 2nd paragraph). Finally, in table 2 Guttman lists the genetically defined forms of Parkinson's disease and parkinsonism which involves gene mutations **PARK genes 1-8** with their specific Gene involved and its clinical characteristics (page 296, table 2).

It would have been obvious to one of ordinary skill in the art to employ rotigotine in prophylactic treatment of Parkinson's disease because rotigotine is effective for the treatment of Parkinson's disease as taught by Shoulson et al early stages of the disease. Moreover, Shoulson teaches that rotigotine did not show statistically significant improvement in advanced PD and will have to be administered with other drugs in advanced PD. Becker, Double et al and Guttman et al teaches the various diagnostic parameters in determining the onset of Parkinson's disease. With regard to the specified subject population not exhibiting symptoms of Parkinson, but having a high

risk set forth in claims 2 not yet having at lest three of four cardinal symptoms including bradykinesia, resting tremors, rigor etc..; a patient having one or more clinical symptoms including movement anomalies set forth in claim 3 a mutation in PARK-gene set forth and/or alternations in the alpha-synuclein or neuromelanin pattern set forth in claim 4; a loss of less than 60% of dopaminergic cells in the substantial nigra set forth in claim 14; a UPDRS score of less than 10 set forth in claim 15; and a Hohn-Yahr score of 0 or 1 set forth in claim 16, they are all obvious because they are all the current evaluation parameters for determining the stages and diagnostic assessment of Parkinson's disease as is well known and taught in above references. One of ordinary skill in the art would promptly evaluate those patients at risk or in at early stages of Parkinson's disease in order to avoid failing of treating Parkinson's disease at their advanced stage. Accordingly, an ordinarily skilled artisan would be motivated to develop a method of treatment of Parkinson's disease at its early stages with rotigotine with a reasonable expectation of success since it has been shown to provide effective decrease in the progression of disease as evidenced by the clinical trials in the prior art.

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Applicant's traversal arguments for this rejection have been fully considered, but are not found to be persuasive.

Shoulson (principal investigator as recited on page 1726) and his study group disclose a controlled trial of Rotigotine Monotherapy in **Early Parkinson's disease (PD) and the study was conducted in patients with early PD** who were diagnosed as having idiopathic PD and had a **Hoehn and Yahr stage of 3.** . Moreover, Shoulson teaches that **rotigotine did not show statistically significant improvement in advanced PD** and will have to be administered with other drugs in advanced PD. As stated by the applicant, prophylactic treatment methods for Parkinson's disease are still unpredictable and there are no therapies available currently which delay the progression of PD. This fact in itself, supported by the positive results shown by Shoulson in early stage PD treatment would motivate an artisan skilled in the pharmacological art to test if the rotigotine would provide any prophylactic benefits. Identification of potential PD markers is well known in the art as taught by Guttman and Double. With that knowledge and knowledge of UPDRS Score and Hoehn Scores, an ordinarily skilled artisan would easily be able to identify a subject at risk of getting PD or in the early stages of PD and with suggestions provided by Shoulson will have a reasonable expectation of success in treating such subjects.

Double Patenting (anticipatory/obvious)

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 3-18 are provisionally rejected on the ground of nonstatutory double patenting over claims 15-24 of copending Application No. 11060997 (copending '997). This is a provisional double patenting rejection since the conflicting claims have not yet been patented. The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application.

The referenced copending application claims a method for treatment or prophylaxis of dopaminergic cell loss associated with Morbus Parkinson's, comprising administration of rotigotine to the subject, wherein the subject is either an (a) individual not exhibiting symptoms but having a high risk of developing Morbus Parkinson or individual not exhibiting symptoms but having a high risk of developing Morbus Parkinson or an individual for whom three of the four cardinal symptoms of Parkinson is not yet present or only partially present. ('997 claims 15-17), Co-pending '997 also

discloses the method of treatment or prophylaxis where in the subject exhibits a mutation in a PARK-gene and/or alteration in the alpha-synuclein or neuromelanin pattern, loss of 60% of dopaminergic cells in the substantia nigra prior, has an UPDRS score of less than 9 and has a Hohn-Yahr score of 0-1 ('997, claims 19-22). Co-pending '997 further discloses that the method comprises administration of rotigotine either by parenteral, transdermal or mucosal administration at a dose of 0.05-50 mg/day ('997, claims 23-24). Morbus Parkinson's is a specie of Parkinson's disease instantly claimed and accordingly, the co-pending '997 claims anticipates the instant claims.

Although the conflicting claims (claims 1-18 in the instant application and claims 15-24, of the co-pending application 11060997) are not identical as stated above, they are not patentably distinct from each other because the claims of the '997 application fully discloses the instantly claimed method of preventive treatment of Parkinson's disease comprising administering to the subject rotigotine.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 5-13 and 17-18 are provisionally rejected on the ground of nonstatutory double patenting over claims 8, 11, and 14 of copending Application No. 10593964 (copending '964). This is a provisional double patenting rejection since the conflicting claims have not yet been patented. The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application.

The referenced copending application claims a method for prevention and/or treatment of a Parkinson's plus syndrome comprising administering to a patient a compound selected from the group consisting of rotigotine, its salts or prodrugs (‘964, claim 1). Co-pending ‘964 discloses a method where in the compound rotigotine is administered orally, parenterally, transdermally or transmucosally ('964, claim 11) and finally co-pending '964 discloses the method wherein the compound rotigotine is administered to provide a dosage of 0.05 mg to 50 mg/ day ('964, claim 14) .

Although the conflicting claims (claims 11, 5-13 and 17-18 in the instant application and claims 1,11 and 14 of the co-pending application 10593964 are not identical as stated above, they are not patentably distinct from each other because the claims of the ‘964 application fully discloses the subject matter of instant claims 1, 5-13 and 17-18. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants have not provided any arguments to overcome this rejection

Conclusion

Claims 1 and 3--18 are rejected. No claims are allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614

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